REMARKS/ARGUMENTS

This response is being accompanied by a petition to revive an abandoned application pursuant to 37 CFR 1.137(b) and a request for filing a continued prosecution application (CPA) pursuant to 37 CFR 1.53(c).

The Claims

Claims 61-68 are currently pending in the application and are directed to a method of treating bone loss by administering an expression vector comprising a nucleic acid encoding osteoprotegerin (hereafter "OPG").

Claim 68 has been cancelled without prejudice or disclaimer.

New claims 69-76 have been added. The new claims are fully supported by the specification and do not introduce new matter or raise new issues requiring further consideration and/or search. Entry of the new claims is respectfully requested.

Rejection under 35 U.S.C. 112

Claims 61-68 are rejected under 35 U.S.C. 112, first paragraph, as the specification allegedly fails to enable one skilled in the art to make and/or use the invention. The Examiner has argued that the specification is not enabling because the claims are directed to somatic cell therapy while the experiments demonstrating *in vivo* expression and activity of OPG were carried out in transgenic mice. The transgenic mouse model allegedly does not enable the claimed invention since nucleic acids encoding OPG were transfected into embryonic cells rather than somatic cells, and the effects of OPG expression were observed in normal mice rather than mice that had experienced bone loss. The Examiner also alludes generally to the unpredictability of somatic cell gene therapy, citing research articles by Verma et al. (*Nature* 389, 239-242 (1997), Eck et al. (in *The Pharmacological Basis of Therapeutics* 9th ed. McGraw-Hill, 1996, pp. 77-101) and Anderson (*Science* 226, 401-408 (1984).

Applicants wish to point out again that the Examiner appears to argue that the claims are directed solely to somatic cell therapy. If this should be the case, Applicants submit that the claims are not limited to somatic cell therapy and there is no basis in the application for such a limitation. Applicants request that the Examiner provide a basis for this apparent interpretation of Claims 61-68. Even though the scope of the claims is being disputed, Applicants nonetheless maintain that the claims are fully enabled even if they are directed solely to somatic cell therapy.

The test for enablement is whether the claimed invention may be carried out without undue experimentation. Various criteria for determining whether experimentation is undue have been set forth in *In re Wands* 8 USPQ2d 1401 (Fed. Cir. 1988). For the reasons set forth below, Applicants maintain that the Examiner has not properly considered the direction and guidance in the specification, the working examples, and the state of the art, and has not properly established a *prima facie* case of nonenablement.

Applicants submit that the specification is enabling for the reasons set forth in the response of September 28, 2001. In particular, Applicants maintain that experiments demonstrating an increase in bone mass in normal animals by administration of an OPG polypeptide or by administration of a nucleic acid expressing OPG (such as in transgenic animals) is clear evidence that OPG acts to inhibit bone resorption. Given the fact that OPG can inhibit bone resorption, one skilled in the art would clearly use OPG as therapy for the treatment of bone loss. While the application discloses the use of OPG in treating bone loss when administered as a protein therapeutic, it is clear that *in vivo* expression of OPG would have the same effect.

The field of gene therapy was clearly established as of 1995 as evidenced by the number of clinical trials approved prior to August of 1994 (see Table 5.1 starting on p. 79 of Eck et al., *supra*). As of 1995, a number of reports indicating success in expressing proteins after gene transfer into mammals had appeared (see, for example, Yang et al. *Critical Rev. Biotech.* 12, 335-356 (1992) cited by Applicants). Applying known techniques for expression of nucleic acids encoding OPG *in vivo* and the success in expressing biologically active OPG *in vivo* in transgenic mice would have would have enabled one to carry out the claimed invention without undue experimentation.

In the Office Action of December 14, 2001, the Examiner argues that "gene therapy and the use of recombinant proteins for therapy are completely different" citing Buckel (*Trends Pharmacol. Sciences* 17, 450-456 (1996)), Anderson, *supra* and Rodan et al. (Science 289, 1508-1514 (2000) for support. Whether gene therapy and protein therapy are different does not, by itself, establish non-enablement. Instead, it must be determined whether undue experimentation would be required to treat bone loss by expression of OPG. As indicated above, given the disclosure of OPG structure and its activity in inhibiting bone resorption in transgenic mice, it would not require undue efforts to treat bone loss by expressing OPG *in vivo*. Indeed, the Rodan article on p. 1512 clearly suggests the use of OPG gene therapy as an alternative to injection of the protein itself.

The Examiner's case for unpredictability of somatic cell therapy rests largely on articles which address the possible lack of therapeutic benefit in some human clinical trials using gene therapy protocols. However, such arguments must be made on a case by case basis as an apparent lack of therapeutic benefit for one type of gene therapy is not *prima facie* evidence for lack of benefit for another type. This is especially true in the present case where *in vivo* expression and anti-resorptive activity of OPG has been clearly demonstrated in the application. Moreover, as indicated below, evidence previously presented in a declaration submitted pursuant to 37 CFR 1.132 clearly shows the therapeutic benefit of *in vivo* OPG expression in an animal model for bone loss.

Should the Examiner establish a *prima facie* case of non-enablement, Applicants have in rebuttal submitted in connection with the response of September 28, 2001 a Declaration by Dr. Jackie Z. Sheng which shows expression of OPG in somatic cells of ovariectomized (OVX) mice infected with an adenovirus associated vector containing OPG cDNA. OVX mice expressing OPG showed a reduction in bone loss compared to OVX mice not receiving OPG vector DNA. These experiments, which were carried out using gene transfer vectors available to the

skilled worker as of the earliest filing date of the application. The experiments overcome the arguments the expression and activity of OPG in somatic cells was not tested, and that *in vivo* expression of OPG was not shown to correct a condition of bone loss. The Sheng declaration clearly shows that the claimed invention may be carried out without undue experimentation using materials and procedures either disclosed in the application or were well known and publicly available as of the priority date of the application.

In spite of the clear evidence presented in the Sheng declaration, the Examiner argues that the declaration is insufficient to overcome the rejection because "the [OVX] mice used in Bolon et al. (Exhibit C, Sheng as senior author) were true mice models for osteoporosis." However, OVX mice were used in the Sheng declaration as well and were prepared in generally the same manner as in the Bolon et al. reference (compare paragraph 6 of the Sheng declaration with the first paragraph of the section entitled "Efficacy bioassay" on p. 198 of Bolon et al.). Since OVX mice were used in the Sheng declaration, there appears to be no basis for the Examiner to disregard the evidence presented therein. It is believed that the declaration is sufficient to overcome the rejection.

CONCLUSION

Claims 61-67 and 69-76 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

67. (amended) The method of Claim 61 wherein the bone loss is due to osteoporosis, Paget's disease, hypercalcemia, hyperparathyroidism, steroid-induced osteopenia, rheumatoid arthritis, osteomyelitis, osteolytic metastasis, or periodontal bone loss.

69. (new) A method for reducing osteoclast activity in a mammal comprising administering to the mammal an expression vector comprising a nucleic acid encoding osteoprotegerin and expressing osteoprotegerin.

70. (new) The method of Claim 69 wherein the nucleic acid sequence is selected from the group consisting of:

a) a nucleic acid encoding a polypeptide comprising the amino acid sequence from residues 1 to 401 or from resides 22 to 401 as shown in Figure 9C-9D (SEQ ID NO:124);

b) a nucleic acid encoding a polypeptide comprising a deletion of 1 to 216 amino acids residues from the carboxy terminus of the polypeptide as in (a); and

c) a nucleic acid which hybridizes under high stringency conditions of 5XSSC, 50% formamide and 42°C with the nucleic acid set forth in (a) and (b) wherein the hybridizing nucleic acid encodes a polypeptide having the activity of reducing osteoclast activity.

71. (new) The method of Claim 69 wherein the nucleic acid encodes a polypeptide comprising residues 22-185, 22-189, 22-194, or 22-201 inclusive as shown in Figure 9C-9D (SEQ ID NO:124).

72. (new) The method of Claim 71 wherein the nucleic acid further comprises an Fc region of human IgG.

73. (new) The method of Claim 69 wherein the expression vector is a viral vector.

74. (new) The method of Claim 69 wherein the expression vector further comprises a pharmaceutically acceptable adjuvant.

75. (new) The method of Claim 69 wherein the mammal has a loss of bone mass.

76. (new) The method of Claim 75 wherein the bone loss is due to osteoporosis, Paget's disease, hypercalcemia, hyperparathyroidism, steroid-induced osteopenia, rheumaotid arthritis, osteomyelitis, osteolytic metastasis, or periodontal bone loss.